CLINICAL PROFILE RISK FACTORS AND OUTCOME OF HIV INFECTED PULMONARY TUBERCULOSIS PATIENTS

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CERTIFICATE

This is to certify that the dissertation entitled **"CLINICAL PROFILE RISK FACTORS AND OUTCOME OF HIV INFECTED PULMONARY TUBERCULOSIS PATIENTS"** is the bonafide original work of **Dr. A.RAMALINGAM,** done by him under my guidance in partial fulfillment of the requirements for MD (General Medicine) branch I examination of The Tamilnadu Dr. M.G.R. Medical University to be held in March 2010. The period of post graduate study and training was from May 2007 to February 2010. I forward this to the Tamil Nadu Dr. M.G.R. Medical University, Chennai, Tamil Nadu, India.

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DECLARATION

I Solemnly declare that the dissertation titled **"CLINICAL PROFILE RISK FACTORS AND OUTCOME OF HIV INFECTED PULMONARY TUBERCULOSIS PATIENTS"** was done by me at Stanley Medical College and Hospital during 2007-2009 under the guidance and supervision of **Prof. RUCKMANI REDDY, M.D.,** This dissertation is submitted to THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY towards the partial fulfillment of requirements for the award of M.D. Degree (Branch-I) in General Medicine.

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CONTENTS

INTRODUCTION

Human Immunodeficiency Virus (HIV) and Tuberculosis (TB) are leading causes of infectious diseases related morbidity and mortality. While one-third of the global population is infected with mycobacterium tuberculosis (MTB), 33 million individuals are estimated to be living with HIV globally (Global HIV report UNAIDS 2008). Approximately 13-15 million HIV infected individuals are estimated to have HIV-TB co-infection (Global TB report WHO 2008). Currently India is estimated to have 2.5 million HIV infected individuals and it also harbours the largest number of TB cases in the world (Global TB report 2008).

Active TB is the commonest opportunistic infection amongst HIV infected patients and is the leading cause of death amongst these patients. TB is one of the most virulent opportunistic infections and it appears early in the course of the HIV infection than other opportunistic infections. As it is one of the first opportunistic infection to appear in HIV-infected people, TB may be one of the earlier signs of HIV infection. HIV specifically eliminates macrophages and CD4 cells that provide immunity against TB thereby fuels

the spread of TB. People with latent TB are increasingly becoming infected with HIV and many more develop active TB because HIV weakens their immune system. People who are co-infected with both HIV and latent TB have greater risk for developing active TB disease and becoming infectious compared to people not infected with HIV. TB in HIV patients has different clinical presentation, hence it can be a diagnostic challenge. TB progresses faster in HIV-infected people. In early stage the presentations of TB in TB-HIV co-infection is the same as HIV-negative but in late stages extra-pulmonary and disseminated forms are more common. The treatment outcome is different and chances of relapse and resistance are also high. TB in HIV is more likely to be fatal if undiagnosed or left untreated.

TUBERCULOSIS[(1)]

Tuberculosis is caused by M. tuberculosis. It is a strict aerobe, obligate parasite. Because of its exceptionally high lipid content the organism is resistant to drying, alcohol, alkali, acids and some germicides. Due to its unusually long doubling time (12-18 hours), growth in culture is slow (3-8 wks). Tuberculosis is transmitted by the airborne route by droplet nuclei. Coughing, sneezing, spitting, singing and other respiratory maneuvers generate droplets nuclei. A bout of coughing produces up to 3500 nuclei, as does speaking for 5 minutes in a normal tone.

PATHOLOGY

Mycobacterium tuberculosis bacilli that reach the alveoli are ingested by alveolar macrophages. The essential pathology in tuberculosis is the production of the characteristic lesion, the tubercle, which is an avascular granuloma composed of central zone containing giant cells, with or without caseation, a peripheral zone of lymphocytes and fibroblasts. Depending on

the time of infection and the type of responses, tuberculosis may be classified as primary and post-primary types.

Primary infection results in the primary (Ghon's) focus, which may be present in any lung zone. The primary complex, the ensuing lymphangitis and hilar lymphadenitis constitute the primary complex. Primary infection heals with or without calcification. Haematogenous spread probably occurs via the lymphatics in the majority of the infected subjects, resulting in the seeding of the tubercle bacilli to other parts of the lung as well as other organs. This stage of infection is usually clinically and radiographically silent.

The infection is contained but not eradicated, since viable organism may lie dormant within the granulomas for years to decades. Individuals with this latent tuberculosis infection (LTBI) do not have active disease and cannot transmit the organism to others. However, reactivation of disease may occur if the host's immune defenses are impaired. Approximately 10% of individuals with LTBI who are not treated will develop active tuberculosis in their life time and half of these cases occur in next two year, following primary infections. Upto 50% of HIV infected patients will

develop active tuberculosis within two years after infection with M. tuberculosis. Diverse condition such as gastrectomy, silicosis, diabetes mellitus, disorders associated with immunosuppression including HIV infection and acquired immunodeficiency syndrome (AIDS), corticosteroid, other immunosuppressant drug use, are associated with increased risk of reactivation of tuberculosis.

In less than 10% of patients, the host immune response is inadequate and progressive primary tuberculosis develops. Reactivation of latent tuberculosis infection is the most frequent (90%) form of post-primary pulmonary tuberculosis. Reactivation pulmonary tuberculosis is most often seen in the upper lung zones most frequently in the posterior segment of upper lobe or the apical segment of the lower lobe. The high ventilation-perfusion ratio, with increased alveolar partial pressure of oxygen relative to other zones is believed to predispose the reactivation at these sites. Proliferation of tubercle bacilli in the caseous centre is followed by softening and liquefaction of the caseous material, which may discharge in to the bronchus with resultant cavity formation. The bacillary load is about 10^4 bacilli per gram in the caseous tissue and upto 10^9 organisms may be found in single cavitary lesion. Rupture of caseous pulmonary focus into arterial

blood may result in military tuberculosis, with the formation of multiple millet sized (0.5-2mm) tuberculosis foci in the lung and various other organs of body.

IMMUNOLOGY

The only specific immune mechanism effective is cell mediated type; humoral immunity appears to be non-protective. The key cell is activated CD4+ T-lymphocytes which can develop along two different paths, namely the Th1 or Th2 cells. Th1 dependent cytokines activate macrophages resulting in protective immunity and containment of infection. Th2 cytokines induce delayed type hypersensitivity which produces tissue destruction and progressive disease.

CLINICAL FEATURES

Tuberculosis disease may manifest in to pulmonary and extra-pulmonary forms. Pulmonary tuberculosis, by far the most common form, can manifest as primary progressive primary and post-primary forms.

Primary Tuberculosis

In the regions with high prevalence, primary tuberculosis is usually seen in children. It is manifested by the primary focus, the inflamed lymphatics and the enlarged regional lymph nodes. Majority of cases are asymptomatic, with the only evidence of infection being the development of positive tuberculin test three to six weeks after infection. Rarely primary infection may progress rapidly to active disease. This may involve local extension in to the lung parenchyma (often with cavitations and/or pleural effusion), systemic dissemination (military tuberculosis and tuberculosis meningitis) and local complications such as enlarged lymph nodes compressing bronchi, causing obstruction and subsequent segmental or lobar collapse, obstructive emphysema and bronchiectasis.

Post-Primary Tuberculosis

Early symptoms and signs of post-primary tuberculosis are often non-specific and insidious, consisting of fever, night sweat, weight loss, anorexia, general malaise and weakness. Most patients develop a cough, which may be non-productive initially later being accompanied by purulent sputum are not infrequent and frank hemoptysis may occasionally occur.

Pleuritic chest pain some times develops in those with subpleural parenchymal lesions but can also result from muscle strain due to persistent coughing. On general physical examination there may be wasting, pallor, and digital clubbing. Respiratory system examination may sometimes be unremarkable. Usually, crepitations may be heard in the affected areas after coughing, bronchial breathing of different characters (tubular, cavernous and amphoric) may be audible depending on the extent of disease.

Drug-Resistant Tuberculosis

Multidrug resistant tuberculosis (MDR-TB) caused by Mycobacterium tuberculosis that is resistant to both isoniazid and rifampicin with or without resistance to other durgs. Extensively drug-resistant tuberculosis (XDR-TB) is defined as resistance to at least rifampicin and isoniazid (which is the definition of MDR-TB), in addition to any fluoroquinolone, and to at least one of the three following injectable drugs used in anti-TB treatment: capreomycin, kanamycin and amikacin, has emerged recently. XDR-TB is associated with a high mortality rate and along with MDR-TB it threatens to jeopardize global TB control. Incomplete

and inadequate treatment is the most important factor for MDR-TB and XDR-TB are manmade disasters.

DIAGNOSIS

Sputum Microscopy

Diagnosis of tuberculosis is established by demonstrating acid-fast bacilli (AFB) on microscopic examination of at least two sputum smears through Ziel Nielson technique. Other staining methods include rhodamine-auromine staining and fluorescence microscopy, a method that is faster and more sensitive. Sputum microscopy usually identifies only half of patients with pulmonary tuberculosis, as at least 10,000 organisms/ml of sputum are required to detect AFB. This is particularly relevant in persons with HIV infection in whom lung cavitations is less common, the yield of smear microscopy is low.

Mycobacterial Culture

Definitive diagnosis of pulmonary tuberculosis depends on the isolation and identification of M. tuberculosis in culture. Sputum mycobacterial culture is more sensitive (80%) than smear microscopy

(<50%) requiring less than 1000 AFB/ml for the diagnosis. In addition, it allows drug sensitivity testing and characterization of the isolates as drug sensitive or resistant. Various media are available for isolating tubercle bacilli. Lowenstein-Jensen egg medium and Kirchner's broth both require up to six to eight weeks for documenting positive growth.

Rapid Diagnosis

Liquid media with radiometric growth detection systems (e.g., Bactec460) and the identification of isolates by nucleic acid probes or polymerase chain reaction (PCR) are also increasingly being used for rapid diagnosis of tuberculosis.

Imaging

Radiographic abnormities in primary pulmonary tuberculosis include small homogenous infiltrates with lymph node (hilar, paratracheal) enlargement and segmental atelectasis. Pleural effusion may be present, especially in adults, sometimes as the sole radiographic abnormality. Cavitation may be seen with progressive primary tuberculosis. Ghon

(calcified primary focus) and Ranke (calcified primary focus and hilar lymph nodes) complexes are evident in some patients.

Reactivation tuberculosis is associated with various radiographic manifestations, including fibrocavitary apical disease, nodules and pneumonic infiltrates. The usual location is in the apical or posterior segments of upper lobes. In elderly and patients with immunocompromised status like diabetes, lower lobe infiltrates with or without pleural effusion is encountered with increased frequency. A military pattern (diffuse small, <2mm, nodular densities) can be seen with haematologic or lymphatic dissemination of the organism. Resolution of reactivation of tuberculosis leaves characteristic radiographic findings such as dense nodules in the pulmonary hila with or without obvious calcification, upper lobe fibronodular scarring and bronchiectasis with volume loss. Radiologically the extent of disease can be classified in to minimal, moderately advanced and far advanced tuberculosis.

Tuberculin Skin Test

In adults, especially in endemic areas, the tuberculin skin test (TST) is of limited value for diagnosis of tuberculosis disease due to low sensitivity

and specificity. TST also cannot distinguish between LTBI and active disease. In addition positive results are found in people who have been sensitised by non-tuberculous mycobacteria or bacilli Calmette-Guerin (BCG) vaccination. False-negative reaction is common in immuno suppressed patients and in patients with overwhelming tuberculosis.

Interferon-γ Based Assays

A significant recent development has been the availability of interferon-γ (IFN-γ) assays based on the principle that T-cells of sensitized individuals produce IFN-γ when they re-encounter the antigens of M.tuberculosis. The IFN-γ assays are available in the enzyme linked immunosorbent assay (ELISA) and the enzyme-linked immunospot (ELISPOT) formats. These assays are not hampered by the limitations of TST and seem to have the potential to replace TST in future.

Other Methods

Serodiagnostic tests cannot reliably distinguish active tuberculosis from infection with M.tuberculosis. Molecular methods such as PCR are hindered by high sensitivity and false positivity.

MANAGEMENT

The World Health Organisation (WHO) recommends directly observed treatment, short-course (DOTS) approach to control TB globally. DOTS strategy which aims at detecting atleast 70% of the existing cases of sputum smear-positive cases and curing at least 85% of these newly detected cases have been observed not only to ensure cure but also reduce the number of deaths due to TB. The Revised National Tuberculosis Control Programme (RNTCP) of India that now covers the whole country, has adopted the WHO recommended DOTS strategy for the control of TB. Recently, the International Standards for Tuberculosis Care (ISTC) has been published. The ISTC were developed to facilitate the effective engagement of all care providers, public as well as private in delivering high-quality care to patients.

All treatment regimens have two phases, namely an initial intensive phase and a continuation phase. The initial intensive phase of treatment is designed to kill actively growing and semi- dormant bacilli and to shorter, duration of infectiousness, usually with rapid smear conversion (80-90%) by two to three months of treatment. The continuation phase eliminates most

residual bacilli and reduces treatment failure and relapse. Treatment can be given daily as well as thrice weekly and the treatment must be supervised. All treatment regimens must be in accordance to standards guidelines.

All patients should be monitored for response to therapy, best judged in patients with pulmonary tuberculosis by followup sputum microscopy (2 specimens), at least the time of completion of the initial phase of treatment (2 or 3 months), at five months and at end of treatment. Monitoring of progress of treatment can also be assessed clinically and radiologically, but they are less reliable.

If relapse occurs in spite of adequate supervised treatment, or after short course of regular treatment the patients should be treated category II treatment. MDR-TB and XDR-TB should be treated at specialised centers equipped with facilities for the treating these dangerous forms of tuberculosis.

HUMAN IMMUNODEFICIENCY VIRUS[2]

HIV belongs to the class Retroviruses and family Lentivirinae. Two types of HIV are recognised viz. HIV-1 and HIV-2. Both viruses have a nucleotide sequence homology of about 45% and differ in geographical distribution, biological and molecular characteristics and extent of transmissibility, though both lead to AIDS. However, HIV-2 has been found to be less virulent, less infective and has a longer asymptomatic phase than HIV-1. HIV-1 has three groups: HIV-1 major group (M) outlier group (O); and new group (N). HIV-1 major group can be further classified into subtypes or classes designated A through H, J and K. such subtypes have envelope gene sequences that vary by 20% or more between subtypes. The subtype C has been primarily reported in India.

STRUCTURE OF VIRUS

The virus comprises of an outer envelope consisting of a lipid bilayer with uniformly arranged 72 spikes or knobs of gp120 and gp41. The glycoprotein (gp) 120 protrudes out on the surface of the virus and gp41 is embedded in the lipid matrix. Interior to lipid bilayer are the matrix; internal capsular and nuclear capsid proteins. The core is a ‘cone’ shaped structure

(capsid) and contains two copies of single stranded RNA and viral enzymes reverse transcriptase, integrase and protease, all essential for viral replication and maturation. Surrounding the capsid is a layer of P17 core Gag protein, which is myristoylated. This P17 protein constitutes the matrix of the virion structure. It is vital for maintaining the integrity of viral particle. The size of HIVgenome is about 9.8 kb. HIV has structural and regulatory genes coding for structural and regulatory products, respectively. Structural genes direct the synthesis of physical components of the virus and are also responsible for viral size, shape, structural integrity and its compartmentalisation in host cell. The regulatory genes direct synthesis of proteins that effect the synthesis of viral components and viral replication. The pol. Env and gag are the structural genes while the enzymes are derived from the regulatory genes.

The high variability of the virus accounts for drug resistance and evasion from immune response. This also poses problems for development of a successful vaccine.

REPLICATION CYCLE

As the virus enters the blood stream, it binds to the CD4 cell receptor on T-lymphocytes via its outer gp 120 cover and enters the cellular cytoplasm, where it uncoats and shed its envelope, viral RNA and the unique enzyme, ‘reverse transcriptase’. This enzyme facilitates conversion of viral RNA into DNA, which is known as pro-viral DNA. The pro-viral DNA then creates a mirror image of itself and with the help of another enzyme called ‘integrase’, unites with the host genome and becomes an integral part of the host cell. It then multiplies repeatedly and produces messenger RNA along with the multiplication of the nucleus of the host cell. The messenger RNA directs the host cell machinery to produce new viral particles, which form new virions with the helps of another enzyme known as ‘protease’. The small virions then bud out of the cell and infect other cells with CD4 receptor. Thus, one infected cell becomes a factory producing large number of HIV viruses. During active stage of HIV infection, around one billion viruses are produced every day.

TRANSMISSION OF VIRUS

The virus can be transmitted by following ways: unprotected sex with an infected person; use of unsterilised needles; transfusion of infected blood and blood products and from an infected mother to her child before, during or after birth.. The source of virus in the new born is multi-factoral. HIV infection can occur via amniotic fluid, genital secretions, maternal blood and also through the breast milk.

NATURAL HISTORY OF HIV/AIDS

Infection with HIV leads to a progressive impairment of cellular immune function, characterized by a gradual decline in peripheral blood CD4+ T-lymphocyte levels, which results in an increasing susceptibility to wide variety of opportunistic viral, bacterial, protozoal and fungal infections and to certain malignancies also. The course of the disease is marked by increasing levels of viral replication, emergence of more virulent viral strains and progressive destruction of immune system. However, the natural history of HIV infection can be changed with better diagnosis, ARV therapy and early treatment and prophylaxis of various opportunistic infections.

PROGRESSION OF HIV INFECTION

Three dominant patterns of HIV disease progression have been described. Almost 80-90% of HIV infected are ‘typical progressors’ with a median survival time of 10 years, approximately. About 5-10% of HIV infected individuals are rapid progressors’ with a median survival time of 3-4 years approximately. About 7-10% of HIV infected individuals do not experience disease progression for an extended period of time and are called ‘long-term non-progressors’ (LTNPs).

PATHOGENESIS

HIV is a polytrophic virus and can infect many cells of the immune system. These include CD4+ T cells, macrophages, dentritic cells, microglial cells and astrocytes in the brain and mucosal cells in the bowel. The CD4 molecule is a major cellular receptor site for HIV. However, certain co-receptors determine tropism for various cell types. A homozygous delta-32 mutation in the genes encoding for the CCR5 co- receptor is associated with resistance to infection. There is a role of endogenous cellular inhibitory factor (APOBEC 3G) in supporting viral replication. Certain viral genes (e.g.vif) inhibits the activity of APOBEC 3G leading to continued viral

replication. Other protective mechanisms including mucosal IgA neutralizing antibody response and high cytotoxic T lymphocytes (CTL) responses have been documented in some seronegative but exposed individuals.

The virus exists in large number throughout the course of HIV infection. The half-life of HIV-1 in plasma appears to be only 1-2 days, and that of infectious virions is in the order of minutes.The rapid turnover of HIV provides the ideal mechanism for producing variants with mutations that confer drug resistance or permit escape from immunologic control of HIV infection.

Apart from direct cytopathic effect of budding out from cell, numerous other mechanisms are known to contribute to HIV associated cell death. These include intracellular accumulation of viral extrachromosomal DNA, changes in cell membranes integrity by HIV envelope proteins, apoptosis (more common in uninfected CD4+ T cells) induced by various viral proteins and cytokine alteration, and superantigen induced up-regulation of cell replication and inducing cell activation associated with apoptosis.

HIV pathogenesis involves three major clinical stages of infection: an early period during which high viral replication takes place, a persistent period during which virus is maintained at a lower threshold primarily by the immune system and symptomatic period during which viral replication reemerges and presages development of disease.

Early period

After viral entry, during the period of primary viraemia there are large number of infected cells in the peripheral blood and high titres of infectious virus in the plasma and the lymphnodes (including the CD4 effector cells in the intestinal lamina propria). This is reflected by p24 antigenemia and high plasma viral load. There is also dissemination of the virus into various compartments including the central nervous system. This robust virus replication is associated with a measurable decrease in the CD4+ T cell counts, reflecting an increased rate of destruction. During this initial CD4 cell depletion the precursors (CD4+central memory T cells) are relatively spared. These viral titres decrease dramatically as effective virus-specific immunity develops in the host. Immunologic mechanisms contributing to initial control of viral replication include HIV specific

cytotoxic T-lymphocyte response, antibody-dependent cellular toxicity and HIV-specific CD4+T cell response. This results in stabilization of viral levels and CD4+ T cell counts at a ‘set-point’ for many years. This set-point is an independent predictor of prognosis, higher the set-point worse the prognosis. Resting memory CD4+ T cells occasionally become infected. These cells constitute the reservoir of latently infected cells, which can reseed the plasma with HIV when stimulated. Other latent reservoirs of HIV include the brain, genital organs (testes) and the kidney. All these reservoirs are established during early infection. Presence of HIV in these reservoirs is the main hurdle for achieving viral eradication.

Persistent period

Despite low level of viraemia, CD4 + T cell decline continues at a rate of 25-60 cells/year during chronic infection. Early in the course of infection, CD4+ memory cells are preferentially depleted but as the disease advances even the CD4+ native cells decline. Cellular destruction, diminished cellular production and cellular sequestration may all be important mechanisms for CD4+ T cell decline. In addition to CD4 + T cell loss, a dramatic increase in CD8 + T cell apoptosis has been noted, despite the fact that HIV does not

infect these cells. This is a common theme in HIV-induced immuno- and neuropathogensis.

The immune system plays a considerable role in determining the viral set point and in delaying disease progression. Humoral and cellular immune responses to HIV is detected during this phase. Antibody levels against HIV are high but they have very weak neutralizing activity. CTL response (mediated by CD8+ T cells) inhibits viral replication by two mechanisms- one, by direct killing of infected cells and second, by producing chemokines that inhibit viral replication.

Symptomatic period

Although the immune system can exert a potent responses against HIV, viraemia persists in the vast majority of untreated infected persons and disease progression occurs. CTL responses decline with time, coincident with progression due to immune exhaustion, lack of adequate T-helper cell function, immune escape, host genetic factors, viral reservoirs and defects in antigen-presenting cells. By the time the individual develops symptoms, CD4+ Tcells counts have usually dropped below 300/mm3 and the HIV in the blood and the lymph nodes has again risen to high levels.

1993 REVISED CLASSIFICATION SYSTEM FOR HIV INFECTION AND EXPANDED AIDS SURVEILLANCE CASE DEFINITION FOR ADOLESCENTS AND ADULTS

CD4+ T Cell Categories (cells/µl)	**A** **Asymptomatic, Acute (Primary) HIV or PGL**	**B** **Symptomatic, Not A or C Conditions**	**C** **AIDS Indicator Conditions**
>500	A1	B1	C1
200 to 499	A2	B2	C2
<200	A3	B3	C3

AIMS AND OBJECTIVES

1. To study the clinical profile of pulmonary tuberculosis in HIV positive patients.
2. To analyse the risk factors and outcome of HIV/TB coinfection in North Chennai suburban population.

REVIEW OF LITERATURE

HIV AND TB CO-INFECTION

PATHOGENSIS

The life time risk for development of active TB in patients infected with TB is 10%. Immunosuppression associated with HIV infection amplifies this risk to 5-16% per year [(3)]. The major feature of HIV induced immunosuppression is loss of the CD4+ helper cells that are important for regulation of cell mediated immunity.

HIV infected patients have increased risk for acquisition of MTB, particularly the MDR/XDR organisms. After infection rapid progression to clinical disease (post-primary TB) has been documented and so is a high risk of reactivation of subclinical MTB infection [(4)]. Finally TB can also occur as an immune reconstitution inflammatory syndrome (IRIS) described later in the review.

Tuberculosis also impacts the course of HIV disease. High HIV viral loads and low CD4 counts have been documented in the setting of active TB[(5)]. The consequence of up-regulation of viral replication results in

emergence of diverse HIV quasispecies. Patients with TB/HIV have higher mortality than those without TB even after matching for CD4 counts.

CLINICAL FEATURES

The clinical features of TB in HIV infection various according to the degree of immune-suppression. When CD4 Counts are high (>350/μl), the features are typical with granuloma formations, upper zone disease in the lungs and less frequent extra-pulmonary TB. However with higher degrees of immune suppression (CD4<350/μl), there is ineffective containment of MTB leading to disseminated disease, more frequent extra-pulmonary disease, impaired granuloma formation and atypical lung involvement [(6)].

Clinical presentation of TB depends on the degree of immune-supression.

TB/HIV : CLINICAL FEATURES

CD4>350	CD4<350
• Classical features	• Atypical features
• Usually pulmonary	• Usually EP, disseminated
• Upper Zone, cavities	• Lower Zones
• ? Opportunistic	• Opportunistic
• Usually reactivation	• Usually re-infection

Tuberculosis could be suspected in an HIV infected patient even when there are features that are not classically suggestive of diagnosis. For e.g. patients with unexplained weight loss, Fever of Unknown origin and severe anaemia / leucopenia could be intensively investigated for TB.

DIAGNOSIS

The traditional methods of TB diagnosis may have lesser sensitivity in the context of HIV. An aggressive approach to get microbiological proof of diagnosis is needed in these settings.

Radiology

As mentioned above HIV infected patients with respiratory TB have a tendency to have more commonly lower lobe involvements, less cavitations and frequently normal chest Xrays, particularly with advanced immune suppression [(7)]. An HRCT thorax has higher sensitivity to pick up both pulmonary and extra-pulmonary disease (mediastinal nodes) that can suggest a TB diagnosis.

Tuberculin test

The tuberculin test has a lower sensitivity to detect latent TB amongst HIV infected patients [(8)]. A lower cut-off of 5mm has been recommended in

situations where TB is non-endemic, although this also has limited value. Anergy associated with HIV infection may lead to false-ve TT[9]. Infection with non-tuberculous mycobacteria and receipt of BCG vaccine may confound the interpretation of a positive TT. Positive TT is not an indication of active TB and thus has no role in this setting.

Sputum smears

The sensitivity of smear evaluation for AFB in the sputum is lower amongst HIV infected patients[10]. In the context of patient not providing a sputum specimen, Broncho-alveloar lavage may increase the yield of finding AFB. However, if a patient has sputum smear negative, BAL does not increase the sensitivity for finding MTB. Alternative methods for sputum processing (concentration methods, short term bleach digestion) or AFB detection (immunofluroescence) may increase the sensitivity of detecting AFB.

Alternative methods

For assessing cell mediated immune response against MTB are the gamma-interferon assays. Antibodies may be an indication of past infection and may have a role for detecting active TB in conjunction with tuberculin testing or gamma-interferon assays. Nucleic Acid Amplification for TB or

Polymerase Chain Reaction (PCR) for MTB have been emerging as an important additional tool for diagnosis of TB.There is a role of PCR in detecting drug – resistant TB, especially rifampicin resistance.

Culture

Culturing MTB is the gold standard for the diagnosis of TB. Traditional methods like the Lownestein-Jenson medium is limited by the long-turnaround time. Radiometric Liquid culturing mediums (BACTEC) have a shorter turnaround time (1-2 weeks) and colonies can be used for speciation and assessing drug sensitivity [(11)].

TREATMENT

TB treatment in HIV positive patients

There is no change in the recommendations for management of TB amongst HIV infected patients [(12)]. Standard short course chemotherapy delivered under direct supervision has similar sputum conversion rates as in the HIV negative population. Malabsorption of anti-TB drugs is common amongst HIV infected patients particularly in advanced HIV disease and with concomitant chronic diarrhoea [(13)].

The role of rifampicin is critical in management and unless there is absolute contraindication rifampicin should be used throughout the duration of TB treatment. This helps in preventing relapses and reduces mortality [14]. However, the mortality on anit-tuberculous treatment (ATT) is higher amongst HIV infected patients that may be related to development of another opportunistic infection while waiting for initiation of antiretroviral therapy (ATT). Once or twice weekly regimens are avoided particularly amongst patients with CD4<100/ μl, as these have been reported to increase the risk of acquired rifampicin resistance [15].

The recommended duration of treatment is 6 months, extended treatment durations are recommended in CNS TB and in patients not receiving pyrizinamide in the intensive phase. The role of fluroquinolones (gatifloxacin and moxifloxcin) in shortening the duration of ATT is under investigation.

There is no evidence for lower tolerability of ATT amongst HIV infected patients however some reports of higher incidence of hepatitis have been published [16].

Adjunctive treatment

Concomitant Co-trimaxozole has demonstrated survival benefit amongst HIV infected patients initiating ATT[17] This is recommended for all HIV-TB co-infected patients irrespective of CD4 counts, however the benefit is greatest when the CD4 counts is less than 200/μl. There is lack of conclusive evidence of efficacy of concomitant multivitamins / micronutrients in the management of TB. Steroids are indicated for tubercular meningitis, pericardial TB, Adrenal TB and in patients with severe TB IRIS. The doses of steroids needs to carefully titrated as rifampicin increases clearance of steroids.

Antiretroviral therapy(ART)

The important issues in concomitant use of ART and ATT are whom to initiate ART in the setting of active TB and what ARVs/ATT to use with reference to drug-drug interaction.

The problems associated with simultaneous initiation of ART and ATT include the increased pill burden compromising adherence, probably

additive toxicities, difficulties in identifying the offending agent in cases of overlapping toxicities, and the development of IRIS.

A recent randomized control trail (SAPIT) demonstrated that in HIV-TB patients with CD4<500/μl, waiting for initiating ART until the completion of the maintenance phase of TB treatment was associated with higher mortality [18]. The trail is on-going to look at mortality outcomes in patients initiating ART as soon as ATT is tolerated versus until completion of intensive phase of ATT. Until further evidence is available it may be prudent to offer ART to all HIV-TB patients with CD4 <350/μl as soon as ATT is tolerated (within 2 weeks) and wait for completion of the intensive phase in patients with higher CD4 counts.

The major issue associated with simultaneous use of ATT and ART is drug reactions and drug interactions. Rifampicin (RMP) is a potent inducer of CyP4503A4 isoenzymes that can reduce the levels of Non-nucleoside reverse transcriptase inhibitors (NNRT) and protease inhibitors (Pls) which are substrates for this enzyme [19,20]. Sub-optimal levels of ARVs lead to rapid selection of drug resistance HIV causing treatment failure and clinical progression. Of all the ARVs only efavirenz levels is not impacted significantly and has excellent long term effectiveness [21]. The current

recommended dose for EFV in patients weighting <65 kgs is 600mg hs. Rifabutin (RBT) is a less potent inducer of the CyP4503A4 enzyme and can be used with all the NNRTIs and Pls [22].

Rifabutin is available in India and is more expensive than rifampicin. The efficacy of rifabutin vis a vis RMP in achieving good TB treatment outcomes is similar although evidence amongst HIV infected patients is insufficient.

ARV Class	Recommended	Alternative
NNRTIs With rifampicin With rifabutin (300 mg od) With rifabutin (450 mg od)	EFV (600 mg or 800 mg hs) NVP (200 mg bid) EFV (600 mg hs)	NVP (200 mg bid) without lead-in dose
Pl/r With rifampicin With rifabutin (150 mg q.3W)	All pl/r contraindicated All pl/r can be used	

TB IRIS

Immune Reconstitution Inflammatory Syndrome (IRIS) is defined as occurrence or worsening of a clinical and / or laboratory parameter despite favourable improvement in HIV surrogate makers (CD4 counts and Plasma HIV viral loads) on ART. TB IRIS is the commonest form of IRIS in the developing world and can occur in 15-20% of patients initiating ART[(23)]. Two forms of IRIS are described.

1.Unmasking IRIS: Emergence of a sub-clinical infection within 3 months of ART initiation. This is usually labeled as ART associated Tb and if the clinical presentation is predominantly inflammatory it is defined as unmasking IRIS.

2.Paradoxical IRIS: Worsening of a controlled TB (on ATT) within 3 months of ART initiation.

The major risk factors for development of IRIS include a CD4 count <50/ μl at ART initiation and shorter time between diagnosis of TB (and ATT initiation) and initiating ART. The commonest clinical presentations of TB-IRIS include inflammatory abscesses, tubercular meningitis/tuberculomas, spinal TB, respiratory TB and TB serositis. The differential diagnosis for TB-IRIS include occurrence of a true OI-TB as a

result of low CD4 counts, failure of ATT (drug resistant TB) and toxicities of ATT/ART. Management of TB-IRIS is guided more by clinical situation rather than evidence from trails. Anti-inflammatory agents are the mainstay of treatment. Steroids (dose and duration depending on clinical response) are used in severe TB-IRIS and ART may be discontinued in life-threatening situation. Finally drainage/aspiration of abscesses is needed frequently for many patients. ATT is also recommended if there is a high index of suspiction for active TB. Though TB-IRIS is associated with high morbidity, only CNS TB has been associated with higher mortality[24].

PREVENTING TB IN HIV INFECTED PATIENTS

The best intervention for preventing the development of active TB amongst HIV infected patients is ART. Studies have documented a decline of 80% in the incidence of TB amongst HIV infected patients on ART[25]. The benefit associated with the use of ART is highest within 3 months of initiation of ART. Another intervention that has been tested for preventing TB is using ATT drugs for treatment of latent tuberculous infection[26]. Isoniazid (INH) for 9-12 months has been shown to be effective in reducing TB incidence amongst TT positive but not in TT negative HIV infected

patients. However INH did not have any impact on death rates in this cochrane review. The duration of protection of INH treatment is 2-3 years and the risk of development of INH resistance is low. The efficacy of INH treatment is further amplified with the use of concomitant ART. Secondary INH prophylaxis to prevent relapses has also been successful in some settings. One of the critical issues in initiating INH is ruling of active TB which can be difficult amongst HIV infected patients.

Recently a TB vaccine (M.vaccae) when combined with INH treatment was shown to reduce the incidence of TB by 37% amongst HIV infected patients[27].

MDR/XDR-TB IN THE CONTEXT OF HIV

The association of MDR/XDR TB with HIV infection is variable, though it is stronger for XDR-TB[28]. A significant proportion of MDR/XDR-TB is associated with exogenous re-infection. Thus improving adherence to ATT may not prevent the emergence of MDR/XDR-TB amongst HIV infected patients. Institutional and even community outbreaks have been documented and drug resistance bacilli are more infectious and pathogenic as compared to the drug-susceptible ones. Even when

appropriately treated including with ART high and rapid mortality is associated with XDR-TB[29].The Principles of management of MDR-TB are the same as in HIV negative patients. Early diagnosis (using rapid methods) is the mainstay. There is very limited evidence on the safety and efficacy of the use of second line ATT drugs along with ART.

METHODOLOGY

PLACE: Chest clinic and Department of Medicine, Government Stanley Hospital.

DESIGN: Observational study

PERIOD: October 2007 to October 2009

SAMPLE SIZE: 21

INCLUSION CRITERIA:

1. Age > 12years
2. Patients who are HIV seropositive with features of pulmonary tuberculosis like fever,cough, loss of appetite and weakness.

EXCLUSION CRITERIA:

1. Patients who show features of Extrapulmonary tuberculosis.

METHODS:

Persons who found to become seropositive for HIV at Voluntary Counselling and Testing Centre were referred to Chest clinic to screen for the presence of tuberculosis. A detailed history of present, past, personal and family was elicited from these patients. They were subjected to general and systemwise examination with careful search for markers of

tuberculosis and HIV. Basic investigations like Hemogram, Urine routine, Renal and Liver function tests were done. Mantoux test, Sputum examination for Acid Fast Bacilli and Chest Xray were carried out according to there symptoms. CD4+ lymphocyte count was measured.

Patients were diagnosed as pulmonary tuberculosis if,

1. Mantoux test showed reading >5mm
2. Sputum examination for Acid Fast Bacilli showed positive
3. Chest Xray showed features of tuberculosis confirmed by radiologist.

Those who showed negative for pulmonary tuberculosis during initial screening were followed for the development of the same. The pulmonary tuberculosis positive patients were started with antituberculous and antiretroviral drugs. They were followed up regularly and observed for drug reactions and interactions. Their outcome was recorded at the end of the treatment. All relevant data were analysed at the end of the study.

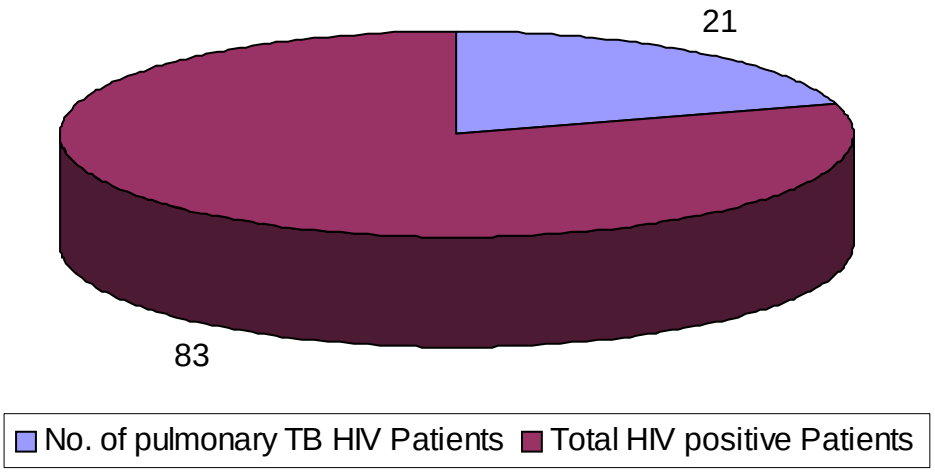
Ethical committee approval was obtained for the study.

RESULTS

PREVALENCE

Out of the 83 confirmed cases of HIV infection, 21 persons found to be suffering from pulmonary tuberculosis. These 21 persons formed the study population.

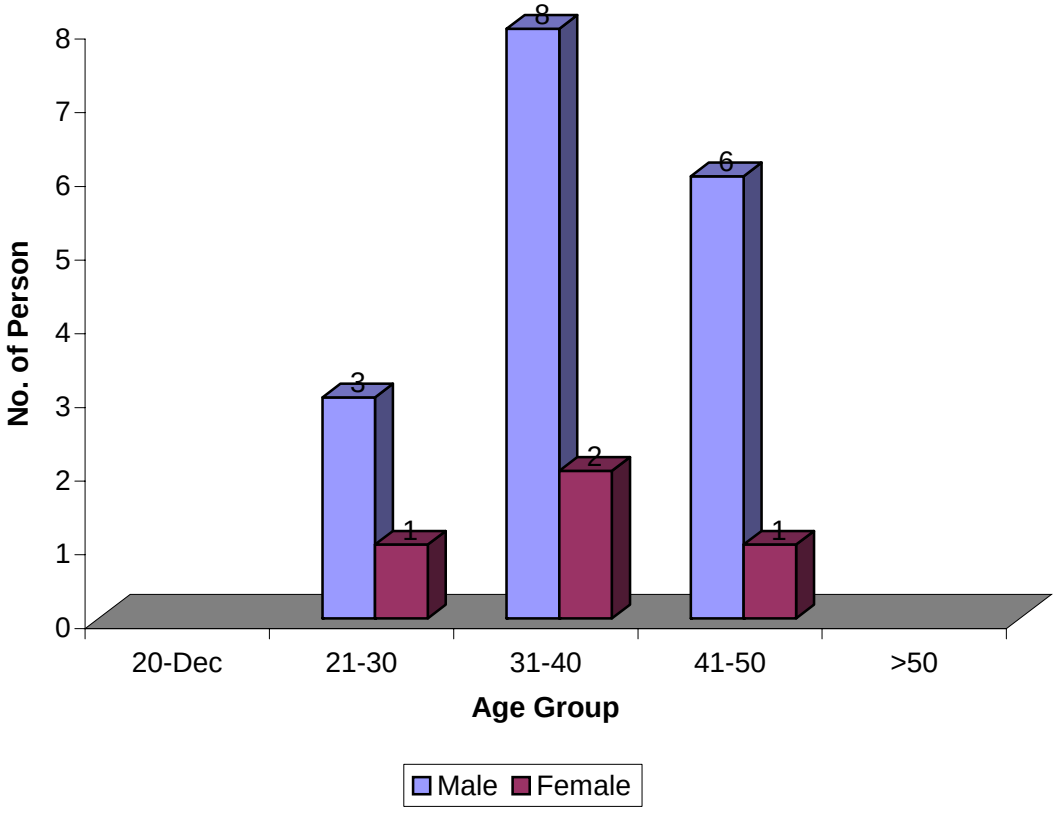
The prevalence of pulmonary tuberculosis infection in HIV seropositive individuals was 21 out of 83 i.e. 25.3%



AGE

The Age-wise distribution of cases as follows

Age Group	Male	Female
12-20	-	-
21-30	3 (14.3%)	1 (4.8%)
31-40	8(38.1%)	2 (9.5%)
41-50	6(28.6%)	1(4.8%)
>50	-	-

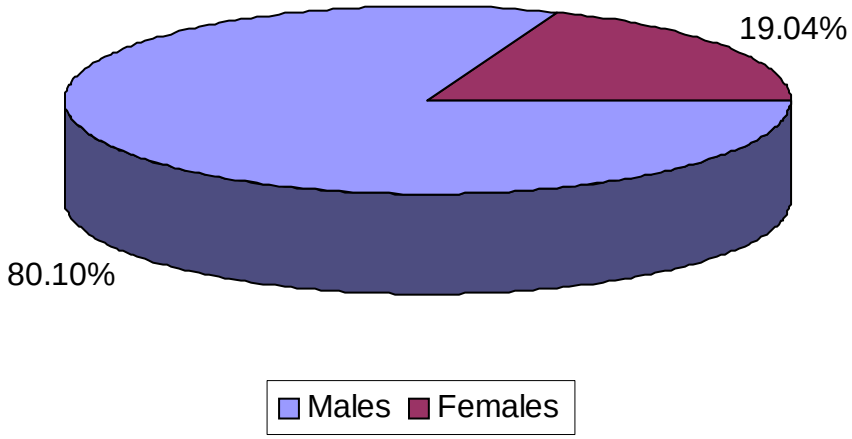


The mean age group in Males : 38.6 years

The mean age group in Females : 39 years

SEX :

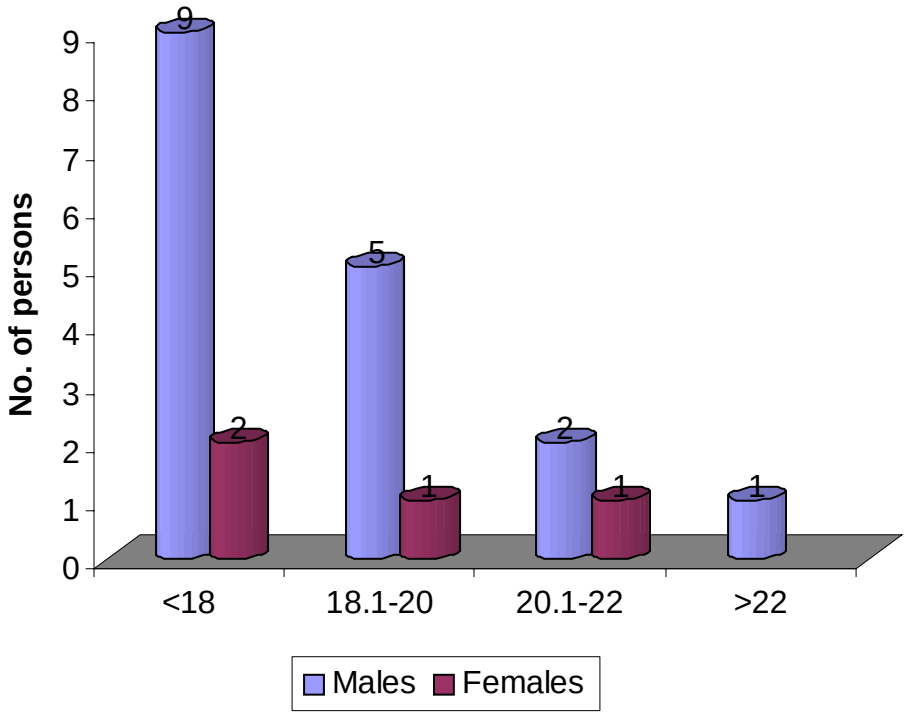
Out of the 21 persons with both pulmonary tuberculosis and HIV, 17 (80.10%) were males and 4 (19.04%) were females.



Body Mass Index :

Body mass index of 21 TB/HIV coinfected persons distributed as follows :

BMI	Males	Females
<18	9(42.8%)	2(9.5%)
18.1-20	5 (23.8%)	1(4.8%)
20.1-22	2(9.5%)	1(4.8%)
>22	1(4.8%)	-



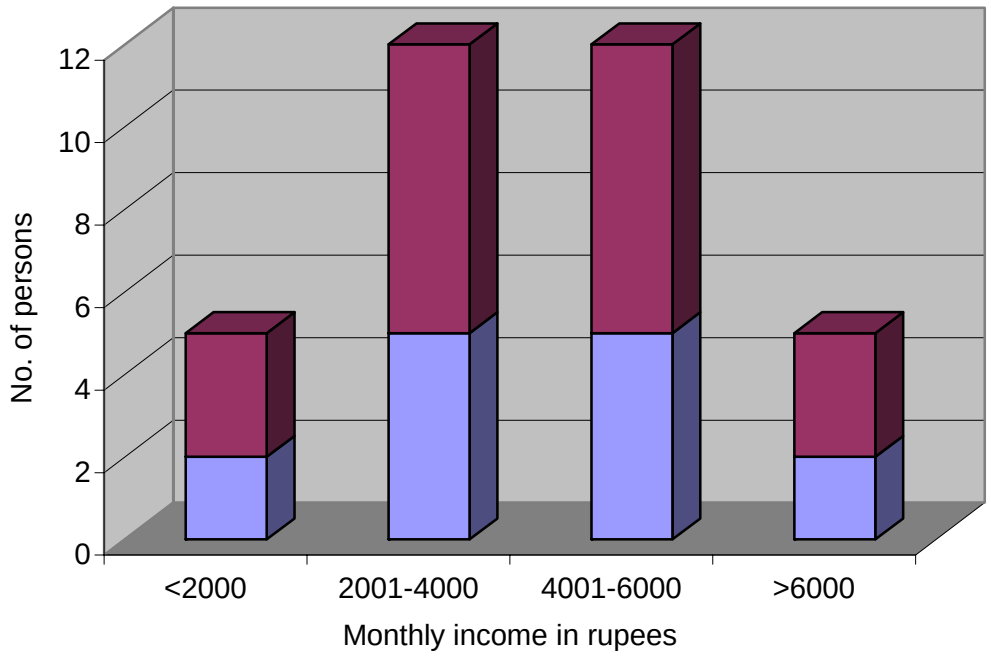
The average BMI for men : 18.9

The average BMI for women : 18.3

OCCUPATION

The following is the distribution of occupation of 21 HIV/TB coinfected persons

Occupation	Male	Female
Skilled Labourers	5 (23.8%)	1 (4.8%)
Drivers	8 (38.1%)	-
Business persons	2 (9.5%)	-
House wife	-	3 (14.3%)
Others	2 (9.5%)	-

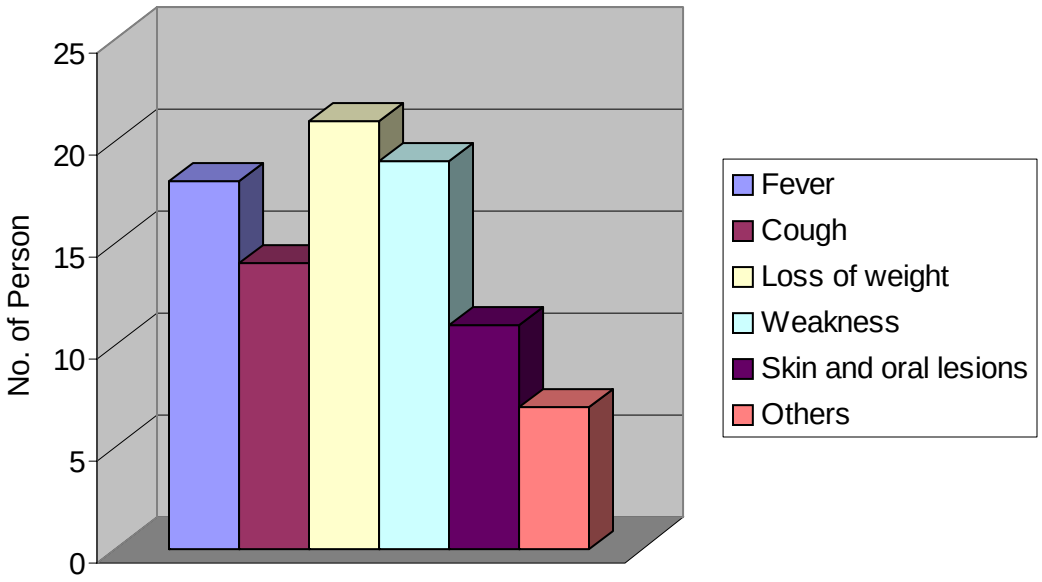


The average monthly income is around Rs.4500/-

CLINICAL FINDINGS

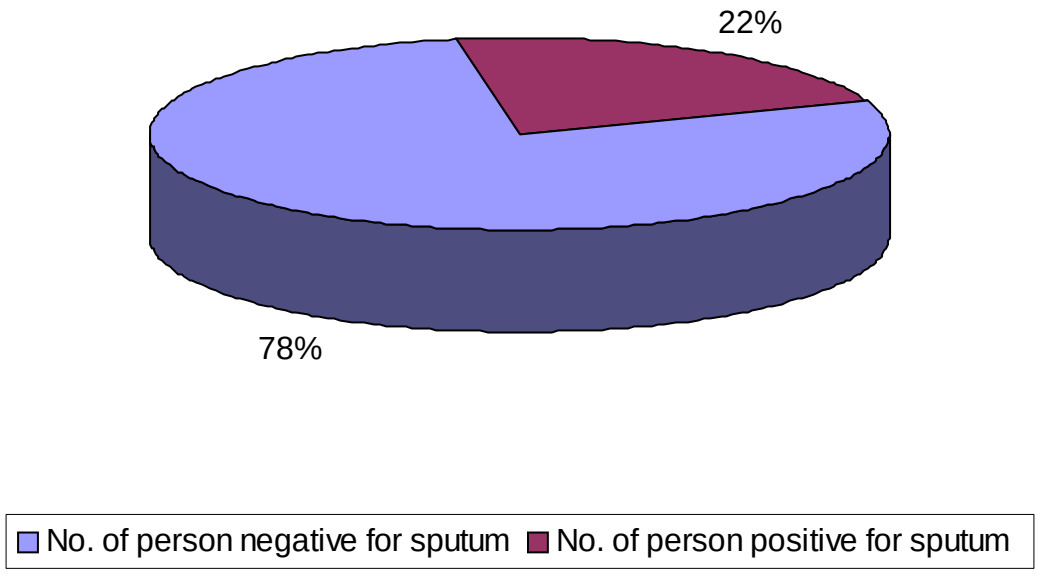
The following is the distribution of clinical presentations of 21 HIV/TB coinfected individuals :-

Clinical Presentation	Number of person
Fever	18 (85.71%)
Cough	14 (66.66%)
Loss of weight	21 (100%)
Weakness	19 (90.47%)
Skin and oral lesions	11 (52.38)
Others	7 (33.3%)



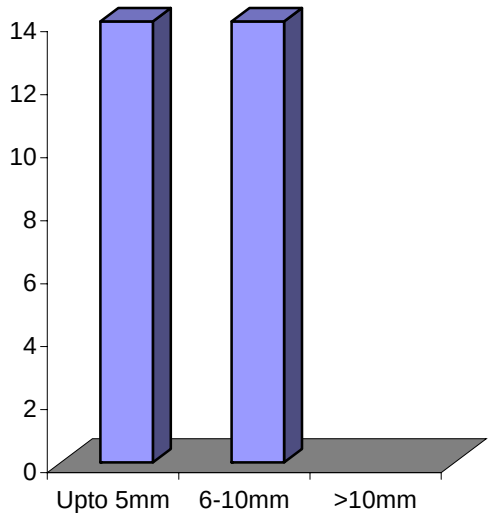
SPUTUM POSITIVITY:

Out of 21(78%) persons, 6 (22%) persons showed positive results in sputum for Acid-Fast bacillus examination.



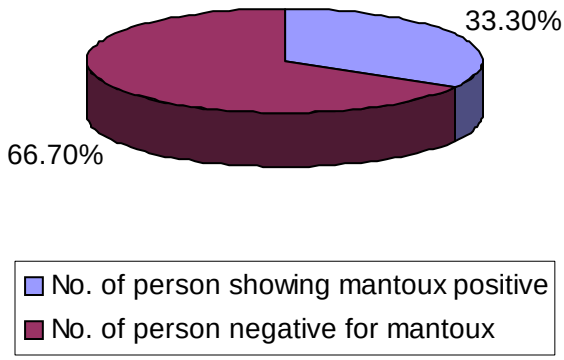
MANTOUX READING :

The distribution of Mantoux reading of 21 HIV/TB coinfected person as follows :



The mean mantoux reading is 3.3mm

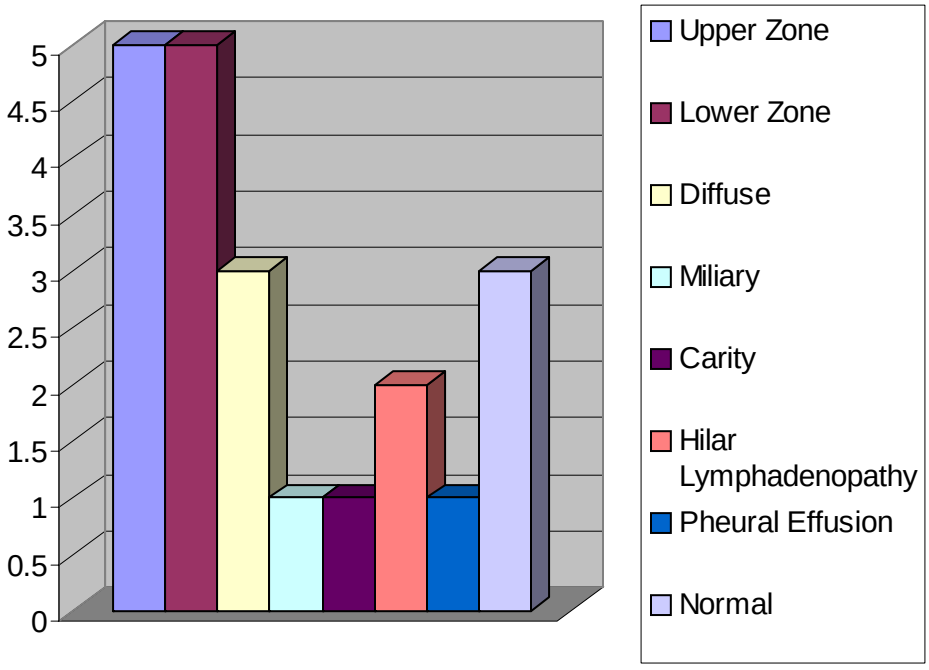
Out of 21 HIV/TB coinfected persons, 7 showed mantoux reading >5mm. The percentage of mantoux positivity in this context is 33.3%



CHEST XRAY FINDINGS

The following is the distribution of chest x-ray findings seen in 21 HIV/TB Co-infected persons:

Xray findings	Number of person
Upper Zone	5 (23.8%)
Lower Zone	5 (23.8%)
Diffuse	3 (14.3%)
Miliary	1 (4.8%)
Cavity	1 (4.8%)
Hilar Lymphadenopathy	2 (9.5%)
Pleural Effusion	1 (4.8%)
Normal	3 (14.3%)

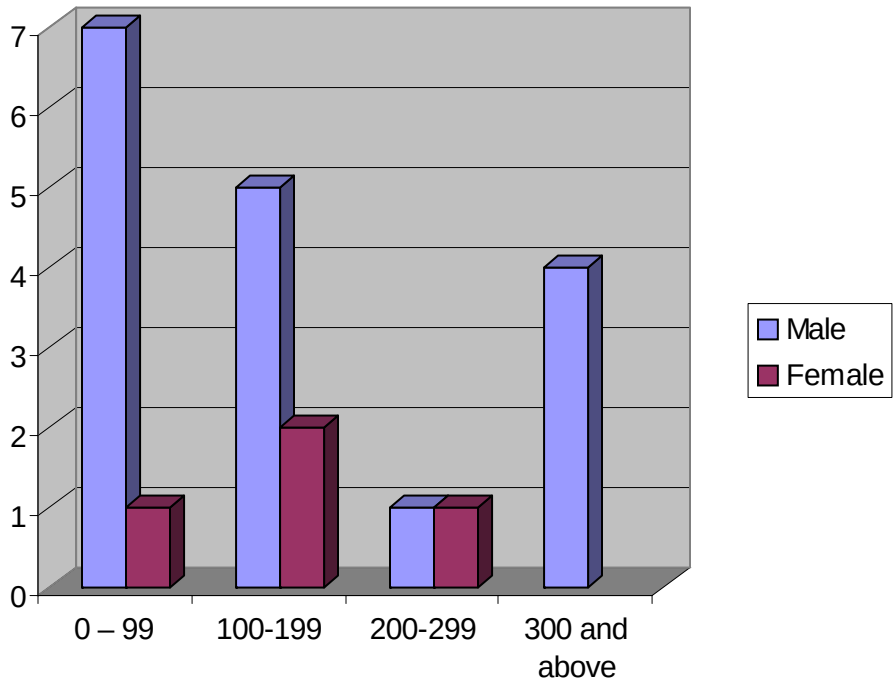


CD4+ Lymphocyte count

The following is the distribution of CD4+ Lymphocyte count of 21 HIV/TB coinfected persons.

CD4+ count(Cells / µl)	Male	Female
0 – 99	7 (33.3%)	1 (4.8%)
100-199	5 (23.8%)	2 (9.5%)
200-299	1 (4.8%)	1 (4.8%)
300 and above	4 (19.04%)	

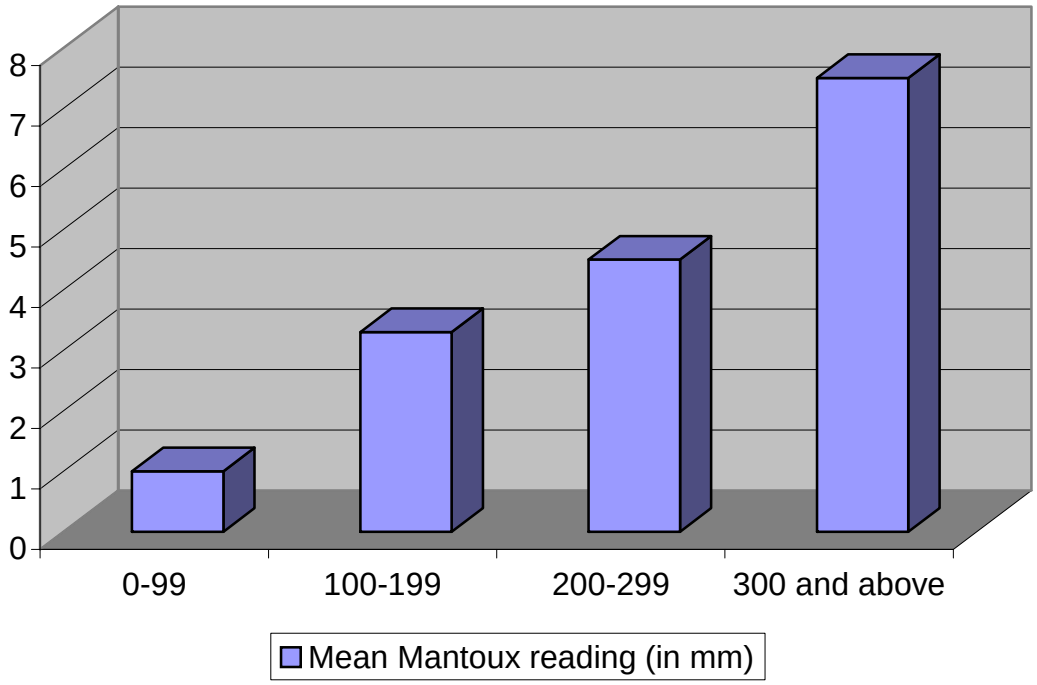
The percentage of CD4+ Lymphocyte count <200 in our study group is 71.4%. The mean CD4 + count is 147 cells/microlitre.



CD4+ Lymphocyte count and Mantoux Reading

The following is the distribution of mantoux reading in various levels of CD4 + Lymphocyte count.

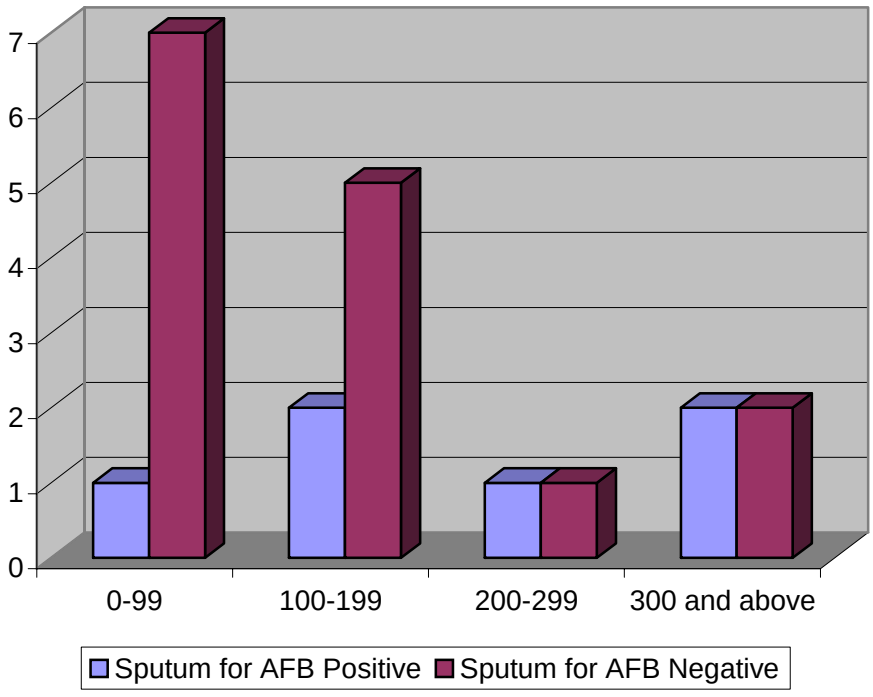
CD4 + Count (Cells / µl)	Mean Mantoux reading (in mm)
0-99	1
100-199	3.3
200-299	4.5
300 and above	7.5



CD4+ Lymphocyte count and Sputum positivity

The following is the distribution of results of sputum examination for acid-fast bacillus of 21 HIV/TB coinfected persons in various levels of CD4 lymphocyte count:

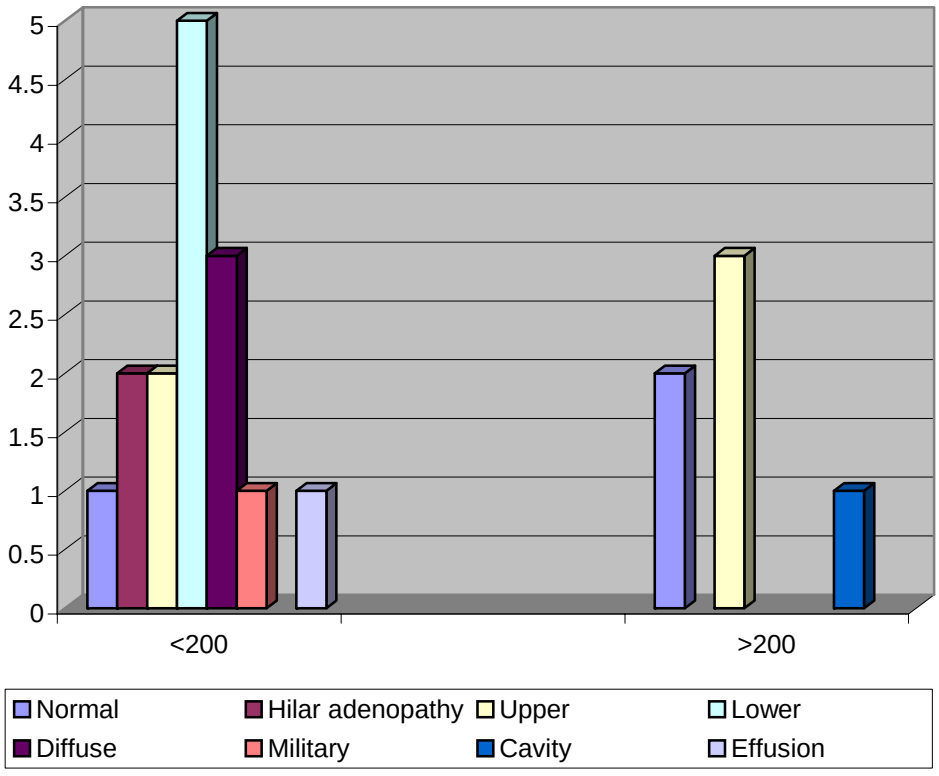
CD4 + Count (Cells / µl)	Sputum for AFB	
	Positive	Negative
0-99	1 (4.8%)	7 (33.3%)
100-199	2 (9.5%)	5 (23.8%)
200-299	1 (4.8%)	1 (4.8%)
300 and above	2 (9.5%)	2 (9.5%)



CD4+ Lymphocyte count and Chest Xray findings:

The following is the distribution of chest xray patterns of 21 HIV /TB coinfection individuals in various levels of CD4 + cents.

CD4 counts	Normal	Hilar adeno-pathy	Upper	Lower	Diffuse	Miliary	Cavity	Effu-sion
<200	1 (4.8%)	2 (9.5%)	2 (9.5%)	5 (23.8%)	3 (14.3%)	1 (4.8%)		1 (4.8%)
>200	2 (9.5%)		3 (14.3%)				1 (4.8%)	

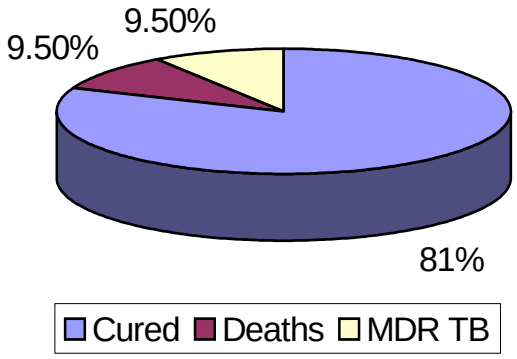


OUTCOME :

All the 21 HIV/TB coinfected persons were started with both anituberculous and antiretorviral therapy and were observed clinically, bacteriologically and radiologically. 17 persons showed improvement and declared cure of pulmonary tuberculosis. 2 person did not improve and diagnosed as multidrug resistant tuberculsosis. 2 persons deteriorated and died during treatment.

The distribution of outcome is an follows :

Outcome	No. of persons
Cured	17 (81%)
Deaths	2 (9.5%)
MDR TB	2 (9.5%)



DISCUSSION

Among 83 patients seropositive for HIV, 21 persons were found to develop pulmonary tuberclosis. The prevalence of pulmonary tuberculosis in HIV infected person was 25.3%[30]. This correlates well with the estimated global prevalence of one third cases of HIV positive patients coinfected with tuberculosis.

The age groups commonly affected by pulmonary tuberculosis among HIV infected persons range from 20 to 50 years. The mean age for HIV/TB coinfection among men and women calculated to 38.6 and 39 respectively. This shows that the sexually active and economically productive group of the population is most vulnerable to HIV/TB coinfection[32].

Out of 21 persons with HIV/TB coinfection, 17 were males and 4 were females. The male to female ratio was 5:1. Males are at higher risk for HIV/TB coinfection[32].

The body mass index calculated for HIV/TB coinfected persons ranges from 16.6 to 22.4. The mean BMI for men and women is 18.9 and 18.3 respectively. This correlates well with the study done by **Vander Saudi MA et al.,**[31] This indicates that lower BMI group is more prone to get pulmonary TB in HIV infection.

Drivers form the most vulnerable group to acquire HIV/TB coinfection. This includes persons who drive autorickshaw, lorry and trailor. High risk behaviours such as sexual practice with commercial sex workers, intravenous drug abuse, alcoholism, matriutrition are seen among this group. Skilled labourers comprises the second largest group to have TB/HIV coinfection[32].

The average monthly income among HIV/TB co-infected persons found to be around Rs.4,500 per month. Thus the lower socioeconomic group is at major risk for coinfection[32].

The most common clinical presentation were fever, cough, weakness and loss of weight[39]. This is comparable to the **registry of AIDS at NACO**

which also shows fever, cough, loss of weight as the commonest symptoms. It seems that HIV does not alter the classical symptoms of TB.

The sputum smear positive for Acid fast bacillus in our study is 28.6%. This is comparable to the results obtained in the earlier studies[32]. In resources limited settings, culture for AFB is not feasible. Moreover, the yield of AFB in HIV infected individuals becomes low due to excretion of fewer organisms per milliliter. This makes very difficult to confirm pulmonary tuberculosis in HIV positive individuals.

The percentage of tuberculin testing positivity is 33.3%. This increased percentage of negativity (mantoux anergy) is comparable to other studies[33].

Atypical chest xray findings are more common in our study population. These included lower zone infiltrations, diffuse, miliary patterns, hilar lymphadenopathy and pleural effusion. This is consistent with other studies[34].

In our study, CD4 lymphocyte count of <200 cells/ µl was observed in 15 out of 21 coinfected persons. This is consistent with the study done by **Alpert et. al.**[35] The mean CD4 + count in our study population is 148 for men and 146 for women. This is consistent with the study done by **whalen et al.**[36]

The relationship between CD4+ count and mantoux reading, sputum positivity, chest xray findings was studied in our 21 HIV/TB coinfected persons[37].

The mean mantoux reading was 2.1mm in <200cells/µl and 6.5mm in >200 cells/ µl. Anergy was noted in CD4 + lymphocyte count of < 200 /µl .

Atypical chest xray patterns such as hilar lymphadenopathy, lower zone infiltration, diffuse & military patterns, effusion were noted in CD4+ count of <200 Cells/ µl

CD4 + Count (Cells/ µl)	**Mantoux reading(mm)**	**Sputum for AFB**	**Chest X-ray**
<200 cells/mm3	Anergy common	Negativity common	Atypical findings common

During the 24 months followup of 83 HIV the cases, 21 became positive for pulmonary tuberculosis diagnosed by either clinical, bacteriological, radiological methods alone or in combination. The risk of getting pulmonary tuberculosis in HIV infected persons is more than that of general population[38].

In our study, out of 21 HIV/TB coinfected persons, 6 fall under category C2 an 15 fall under category C3. The percentage of C2 category is 28.5% and the percentage of C3 category is 71.5%.

All the 21 persons were started with antituberculous and antiretroviral therapy. 19 were under Cat I and 2 under Cat II. No major adverse reactions were noted. Nausea and vomiting were the most common side effects. Among 21 cases, 17 were declared cure with antituberculous therapy in the form of sputum conversion, improvement in both clinical and radiological context. 2 persons deteriorated during treatment and died. 2 persons did not show improve during treatment and were referred to thoracic research center, chetpet, chennai and declared multidrug resistant tuberculosis.

CONCLUSION

1. Pulmonary tuberculosis is more commonly seen in HIV infected individuals.
2. Pulmonary tuberculosis is most commonly seen in third and fourth decade.
3. Males are commonly affected that females.
4. Body mass Index of around 18 is more prone to have pulmonary tuberculosis.
5. Drivers, skilled labourers and low income group were commonly affected.
6. The most common symptoms observed were fever, cough and loss of weight.
7. There is increased incidence of mantoux anergy, sputum negativity, atypical chest xray findings were noted in HIV positive individuals especially in the lower CD4+ count.
8. The risk of acquiring pulmonary tuberculosis is greater in HIV positive person than the general population.
9. The risk of drug resistant tuberculosis is increased in HIV/TB coinfection.

11. Prompt diagnosis and timely administration of ATT and ART therapy results in effective cure of pulmonary TB in HIV positive individuals.

Unless properly managed, the negative synergy between TB and HIV threatens to become a major public health problem in future. Fortunately effective interventions are available for both; however integration of these interventions in clinical care and programs is critical. The emergence of MDR/XDR-TB is an ominous sign, control of which needs a refocus on hitherto neglected infection control practices apart of ensuring proper use of ATT. Improvements in both ATT and ART drugs is needed to shorten the duration of TB treatment, with no drug-drug interactions, and very minimal toxicities so that treatment for both diseases can be optimized.

PROFORMA

- NAME :
- AGE :
- SEX :
- OCCUPATION :
- MONTHLY INCOME :
- Ht(cm) :
- Wt(kg) :
- BMI(kg/m^2) :
- CLINICAL PRESENTATION:

cough/expectoration

fever/evening rise of temperature

loss of appetite/loss of weight

hemoptysis

diarrhea/others

- PAST Hx:
- DRUG ABUSE :
- FAMILY HISTORY :
- GENERAL EXAMINATION

  Built/ skeletal appearance

  anemia/jaundice/cyanosis/clubbing/

  lymphadenopathy/pedal edema/JVP/

  vitamin deficiencies and

  markers of TB & HIV

  VITALS : Temperature/Pulse/BP/RR

  CVS : Apical impulse/heart sounds/others

  RS : Tracheal position/air entry/breath sounds/others

  P/A : Organomegaly/mass/free fluid

  CNS : ALOC/neurological deficit/meningeal signs

- INVESTIGATIONS

  CBC : TC, DC, ESR, Hb, Platelets,PS

  RBS, Urea, creatinine, electrolytes

  Liver function tests

  Urine R/e

  Sputum for AFB (3 samples)

  Mx test

  Chest X Ray

  CD4+ count

  CONSENT

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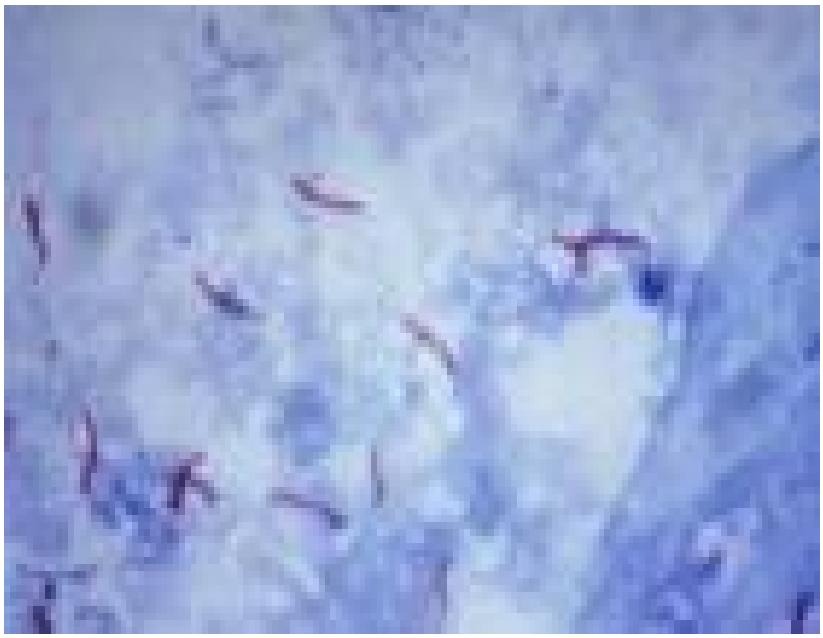

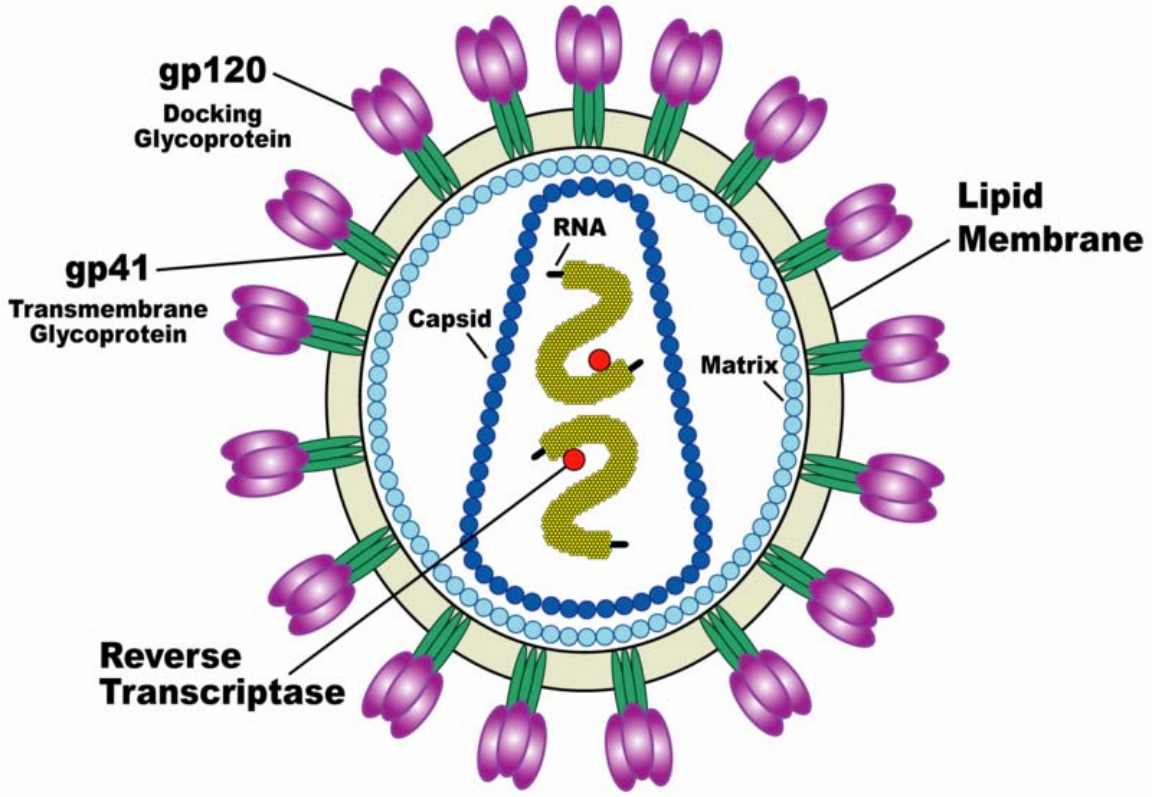
gp120
Docking
Glycoprotein
gp41
Transmembrane
Glycoprotein
Reverse
Transcriptase
RNA
Capsid
Matrix
Lipid
Membrane

MASTER CHART

S. No.	Name	Age	Sex	BMI	Occupation	Monthly income (Rs)	Clinical presentation						Past history	Mx (mm)	Sput-um for AFB	Chest X-ray	CD4 cell/ µl	Clini-cal stagi-ng	ATT cate-gory	outcome
							Fev -er	Cou -gh	Loss of wt	Weak ness	Skin oral	Others								
1	Velu	42	M	20.8	Tailor	6000		4	4	4	4	Hemo-ptysis		3	+ve	Normal	88	C3	I	Cured
2.	Ramesh	33	M	21.3	Mason	4500	4		4	4	4			8		Hilar	156	C3	I	Cured
3.	Vijay	27	M	17.6	Autodriver	3500	4	4	4	4	4			nil	-ve	Diffuse	40	C3	I	MDR TB
4.	Alimudheen	38	M	17.5	Shopkeeper	5000	4	4	4	4				nil	-ve	Lower	38	C3	I	MDR-TB
5.	Nagaraj	37	M	17.7	Harbour Cooly	3000	4		4	4			PT	7		Upper	320	C2	II	Cured
6.	Latha	30	F	19.1	Skilled Labourer	2500	4	4	4	4	4			6	+ve	Diffuse	161	C3	I	Cured
7.	Raja	50	M	21.9	Lorry Driver	5500	4	4	4	4				5	-ve	Upper	327	C2	I	Cured
8.	Pandurangan	46	M	18.8	Auto Driver	4800	4		4	4			IV drug abuse	Nil		Hilar	136	C3	I	Cured
9.	Kiruba	38	F	16.6	Housewife	6000	4	4	4	4	4	Diarrhe-a		Nil	-ve	Lower	28	C3	I	Died
10.	Kannan	46	M	18.0	Auto driver	3000	4	4	4	4	4	Abd-pain	IV drug abuse	5	-ve	Diffuse	58	C3	I	Cured
11.	Damodaran	36	M	19.5	Trailor Driver	4500	4	4	4		4	Abd-pain		7	+ve	Normal	313	C2	I	Cured
12.	Narasimhan	38	M	22.4	Lorry Driver	5000		4	4					10	+ve	Cavity	365	C2	I	Cured

13.	Elumalai	38	M	16.9	Taxi Driver	3500	4	4	4	4	4	Diarroea	PT	Nil	-ve	Miliary	24	C3	II	Died
14.	Kandhan	38	M	17.7	Vendor	2000	4		4	4	4			4		Lower	118	C3	I	Cured
15.	Munusami	45	M	17.5	Business	6000	4	4	4	4	4	Abd-pain		Nil	-ve	Lower	13	C3	I	Cured
16.	Babu	39	M	18.0	Lorry Driver	4500	4	4	4	4		Scrofula		Nil	+ve	Effusion	114	C3	I	Cured
17.	Lingam	48	M	17.6	Mason	4000	4		4	4	4	Abd-pain		Nil		Lower	13	C3	I	Cured
18.	Mani	28	M	19.0	Business	6000	4		4	4				Nil		Upper	182	C3	I	Cured
19.	Jayalakshmi	50	F	20.3	House wife	2000	4	4	4	4				6	-ve	Upper	188	C3	I	Cured
20.	Kalaiselvi	38	F	17.6	Housewife	3200	4	4	4	4				Nil	-ve	Upper	207	C2	I	Cured
21.	Selvam	27	M	19.3	Scrap cleaner	2000		4	4	4	4	Diarrhea		9	+ve	Normal	213	C2	I	Cured